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Caffeine and Pregnancy

Vol 6#1, October 1997

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Caffeine is considered the most widely used drug in the world; an average adult consumes between three and five cups of coffee each day. Significant amounts of caffeine are found in colas, tea, coffee and some prescription medications. In 1980, the U.S. Food and Drug Administration (FDA) cautioned women against caffeine intake during pregnancy based on information from animal studies. Since that time, numerous human studies demonstrate conflicting results on the teratogenicity of caffeine (Julien, 1995). It is estimated that 70-80% of women consume some caffeine while pregnant (Pastore & Savitz, 1995). This RISK||NEWSLETTER will address the effects of maternal caffeine exposure on various aspects of pregnancy.

BACKGROUND INFORMATION

Caffeine, a psychostimulant that acts on the cerebral cortex, increases mental alertness, wakefulness and restlessness. Excessive caffeine intake can result in agitation, anxiety, rapid breathing, tremors, cardiac arrhythmia and insomnia. Caffeine acts within the central nervous system (CNS) to target and block adenosine receptors. This increases the amount of available neurotransmitters, especially dopamine, and accounts for the behavioral effects of caffeine (Julien, 1995).

An average 5 ounce cup of brewed coffee contains 100 mg of caffeine; instant coffee averages less caffeine and espresso coffee averages twice as much caffeine. Tea typically contains 50 mg of caffeine per five ounces, while colas contain about 40 mg of caffeine per 12 oz. serving. In contrast, a one ounce semi-sweet square of baking chocolate contains 25 mg of caffeine (Julien, 1995). These estimates vary widely due to differences in food and beverage preparations.

In humans, caffeine normally has a half-life of three hours. During the first trimester of pregnancy, however, the half-life of caffeine increases to 5.6 hours, and continues to increase to a high of 18 hours by the 35th week of pregnancy (Golding, 1995). These altered pharmacokinetics may be due to changing hormone levels during pregnancy (Berger, 1988). Changing levels and the efficacy of the p450 enzymes may also be involved in altered caffeine half-life (Nolen, 1988). The half-life of caffeine in newborns can be as long as 40-130 hours because of the immature metabolic pathways utilized in caffeine excretion (Nehlig and Debry, 1994a).

Caffeine metabolism differs in animals and humans. In rodents, 40% of caffeine is metabolized into trimethyl derivatives such as methylxanthine; this pathway accounts for only 6% of caffeine metabolism in humans. The main metabolite in monkeys is theophylline. In humans, between 72 and 80% of caffeine undergoes 3-methyl demethylation resulting in paraxanthine formation (Nehlig and Debry, 1994a). This difference makes the applicability of animal studies to humans questionable.

RISK OF CONGENITAL ANOMALIES

Animal studies have shown an increased incidence of birth defects when caffeine is administered to rodents in a large bolus, usually 250 mg or more. Such high caffeine doses are typically associated with delayed skeletal ossification, palate malformation, and missing digits (Nehlig & Debry, 1994a). Primate studies have shown an association with spontaneous abortion (SAB), stillbirth, decreased weight gain and low birth weight (Gilbert et al., 1988). Based on these associations, in 1980 the FDA released a warning statement for caffeine even in the absence of substantiating human data.

Despite the FDA statement, most studies performed after 1980 did not show an increased risk for congenital malformations when caffeine was ingested in moderate amounts by humans. Studies on caffeine prior to the 1980 FDA statement were often fraught with methodological flaws (Nolen, 1988); therefore, the focus of this newsletter will be on studies conducted after 1980.

The first well-controlled study of caffeine use in pregnancy followed 12,205 women who had ingested caffeine during pregnancy (Linn et al., 1982). No increased risk of birth defects due to caffeine exposure in the first trimester was found, including 595 women who drank more than four cups of coffee per day. In a case-control study published the same year, 2,030 women whose children had been born with either inguinal hernias, oral clefts, congenital heart disease, pyloric stenosis or neural tube defects were contacted within six months post-delivery to assess maternal caffeine consumption. Their caffeine intake was compared with 172 controls consisting of children born with birth defects other than those listed above. Caffeine exposure was categorized as less than three cups per day or four or greater cups per day; neither group showed an increased association with malformations (Rosenberg et al., 1982).

Literature review of caffeine exposure during pregnancy consistently show no increased risk of birth defects when caffeine is consumed in moderation (Narod et al., 1991; Nehlig & Debry, 1994a; Golding, 1995). There is, however, controversy over the definition of "moderation." Some authors define moderation as <300 mg of caffeine per day (Nehlig & Debry, 1994a), while others use <200 mg per day (Narod et al., 1991). Little is known, however, about the teratogenic risk of higher levels of caffeine. It is estimated that a woman would have to drink 10-14 cups of coffee in one sitting to begin to reach the doses which have teratogenic effects in animals (Nehlig & Debry, 1994a).

Since their initial statement in 1980, the FDA has modified its policy statement on caffeine, indicating that they are significantly less concerned about the teratogenicity of caffeine in humans (Lecos, 1987). The focus of research since that time has been quantification of risk for spontaneous abortion, intrauterine growth retardation (IUGR), low birth weight (LBW), premature birth and decreased fecundity due to caffeine exposure.

RISK OF SPONTANEOUS ABORTION

The association between caffeine and spontaneous abortion remains unclear. Mills et al. (1993) followed 431 women who were participating as controls in a study of diabetes in pregnancy. Most women in the study consumed 3 or less cups of coffee a day. No significant correlation between first trimester caffeine intake and miscarriage was found. In the same year, Infante-Revard et al. (1993) found an association between caffeine intake and miscarriage. The study population consisted of 331 women who had a recognized miscarriage and were ascertained at a hospital in Montreal. Controls (N=993) at the same stage of pregnancy were located through the hospital when they came in for routine blood work related to their pregnancy. Results showed that for every 100 mg of caffeine consumed per day, the odds ratio (OR) for miscarriage increased by a factor of 1.10. Therefore, if a woman consumed 300 mg of caffeine per day, her risk to miscarry is increased to an OR of 1.35. These two discrepant studies may be explained in part by their ascertainment of patients. Infante-Revard et al. (1993) only followed women who presented for medical care after a miscarriage, while Mills et al.

(1993) involved a natural study population.

Before any conclusions can be drawn concerning caffeine and spontaneous abortion, additional studies controlling for nausea should be undertaken. Nausea level may confound the baseline levels of caffeine consumption in spontaneous abortion studies. This is because women who miscarry are less likely to feel nauseated, and in turn are less likely to decrease caffeine consumption on their own accord (Eskenazi, 1993).

RISK FOR IUGR, LBW, PRETERM LABOR

Most studies examining the association between maternal caffeine exposure and risk for growth delay and preterm labor suggest a low increase in risk, if any is noted. It appears that fetal growth is affected by maternal caffeine consumption only at very high levels. Fenster et al. (1991) found that women who consumed >300 mg of caffeine a day were more likely to have a fetus with IUGR (OR 2.9; 95% C.I. 1.23-6.87). On the other hand, neither Shu et al. (1995) nor Mills et al. (1993) found an association with IUGR. Shu et al. (1995) followed 712 pregnancies for smoking, alcohol and caffeine exposure; when controlled for smoking and alcohol exposures, there was no relationship between caffeine levels and IUGR. This study may not be generalizable to populations with high caffeine intake since only 19 of the women drank more than 3 cups of coffee a day. Mills et al. (1993) tracked birth weight and head circumference to assess growth during the fetal period. No association was found when smoking was controlled, even at levels of >300 mg per day.

Vlajinac et al. (1997) studied the caffeine consumption of 1,011 women in the third trimester and found that an average consumption level >71 mg per day was significantly related to LBW in non-smoking mothers. In women who consumed >141 mg per day, an average reduction in birth weight of 114 grams was found. A dose response relationship between coffee consumption and decreased birth weight was seen in this population. Fenster et al. (1991) found women with increased caffeine intake had a slightly increased risk to have a fetus with LBW (OR 2.05; 95% C.I. 0.86-4.88). Narod et al. (1991) also observed that caffeine may exert a small effect on birth weight.

Preterm birth has also been associated with excessive caffeine use. A study of 12,205 women showed a trend toward increased risk for preterm birth (OR 1.19; 95% C.I.; 0.86-1.65) when smoking was controlled (Linn et al., 1982). However, no dose-response relationship was seen in the first or second trimester in a study of 408 women, thereby reducing the likelihood of caffeine being the causal factor in preterm birth. A non-significant trend was noted in the third trimester between increased caffeine consumption and preterm birth (Pastore & Savitz, 1995). Fenster et al. (1991) found no association between maternal caffeine intake and preterm birth.

RISKS OF DELAYED CONCEPTION

Current research is examining the possible effect of caffeine on the ability of a woman to become pregnant. Initial concern was generated by a 1988 study by Wilcox et al. which found a dose-response effect between caffeine exposure and delayed conception. The 104 women studied were categorized into low or high caffeine consumption, with high caffeine being more than one cup of coffee per day. In this study, high caffeine drinkers were half as likely to conceive per menstrual cycle. After 13 menstrual cycles heavy caffeine drinkers were 4.7 times more likely ($p < 0.005$) to experience delayed conception than low caffeine drinkers.

More recent studies found an effect only when caffeine levels are above 300 mg a day. A European multicenter study on infertility and subfecundity in 3,817 women found that for women who drank more than 500 mg of caffeine a day, there was an increased risk of subfecundity in their first pregnancy (OR 1.45; 95% C.I.; 0.92-2.63). While neither group was significant, the risk was somewhat higher for smokers (OR 1.56; 95% C.I.; 0.92-2.63) than non-smokers (OR 1.38; 95% C.I.; 0.85-2.23). These

findings led the authors to conclude that fertile women who ingest high levels of caffeine may increase their waiting time for conception (Bolumar et al., 1997). Stanton and Gray (1995), however, did not see an association between caffeine and delayed conception in women who had <300 mg of caffeine per day. In non-smokers who had >300 mg of caffeine per day, the likelihood of delayed conception was significantly increased (OR 2.65; 95% C.I.; 1.3-2.37). No significant increase was noted in smokers who consumed the same level of caffeine.

RISKS WITH CO-EXPOSURES

The teratogenicity of caffeine in combination with other drugs merits further investigation. Maternal smoking has been shown to decrease birth weight and increase the risk of preterm birth by 40% (Wisby et al., 1996). These effects may be exacerbated by high levels of caffeine, as previously described (Shu et al., 1995). However, the combination of caffeine and nicotine was not found to significantly exacerbate the increase in LBW already associated with smoking (Vlajinac et al., 1997). A recent British study of 4,111 women found a 3 fold increase in the number of preterm births for mothers who both smoked and consumed >400 mg of caffeine a day, as compared to women who smoked but consumed <400 mg of caffeine per day (Wisby et al., 1996). The teratogenic effects of alcohol may also be increased by the presence of caffeine. Migraine medications such as ergotamine and propranolol are also of concern. In combination with caffeine, these agents may cause vasoconstriction, thereby cutting off oxygenated blood flow to vital tissues (Nehlig & Debry, 1994a). Caffeine may also potentiate the teratogenic effects of radiation (Nolen, 1988). No large-scale human studies investigating the synergistic effects of caffeine with other drugs have been conducted.

RISK TO THE NEONATE

Exposure to significant levels of caffeine in utero has been associated with neonatal withdrawal symptoms including irritability and vomiting. Symptoms typically resolve within several days. Symptoms of withdrawal have not been observed in neonates exposed to moderate levels of caffeine (<300mg) (Nehlig & Debry, 1994a).

Case reports indicate a possible increase in cardiac arrhythmias in newborns born to mothers who ingested very high levels of caffeine during pregnancy. These arrhythmias resolved upon cessation of caffeine exposure (Oei et al., 1989). When caffeine was used to treat apnea or other breathing problems in newborns, some children became irritable, jittery and vomited until caffeine levels were reduced (Nehlig & Debry, 1994a).

A long-term study of 500 children exposed to caffeine in utero measured their development at 4 and 7 years of age. No negative effects from caffeine exposure were found (Barr & Streissguth, 1991). Nehlig and Debry (1994a) conclude that long-term neurobehavioral effects in children exposed to caffeine in utero are unlikely.

BREAST FEEDING

Caffeine is excreted in breast milk. The concentration of caffeine in breast milk is about 1% of that found in the mother's plasma (Berger, 1988). Peak concentration levels of caffeine occur about 1 hour after ingestion. Iron levels in breast milk may also be decreased if the mother is consuming more than 300 mg of caffeine per day. Irritability and insomnia can occur in infants whose mothers ingest high levels of caffeine. Nehlig and Debry (1994b) suggested that by limiting coffee consumption to 1 cup a day, neonatal side effects can be avoided, while Berger (1988) suggested that the maximum range for caffeine consumption should be 200-336 mg per day in women who are breast-feeding.

SUMMARY

Reducing caffeine intake during pregnancy is recommended. When used in moderation (<300 mg per

day), there appears to be little, if any, teratogenic risk. The teratogenic risk from higher levels of caffeine exposure has yet to be determined, although a possible increased risk for SAB, low birth weight, preterm birth, delayed conception and neonatal withdrawal symptoms has been reported. It has also been recommended that caffeine ingestion be reduced during breast feeding.